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AMENDMENT UNDER 37 C.F.R. §1.116
EXPEDITED PROCEDURE
GROUP 1623
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

DAWSON, CHANDLER R., et al.

Docket No: A8285

Appln. No.: 09/767,943

Group Art Unit: 1623

Confirmation No.: 2773

Examiner: Peselev, E.

Filed: January 24, 2001

For: TOPICAL TREATMENT OF PREVENTION OF OCULAR INFECTIONS

DECLARATION UNDER 37 C.F.R. §1.132

ATTN: BOX AF
Commissioner for Patents
Washington, D.C. 20231

I, Lyle M. Bowman, hereby declare and state:

I graduated from the University of Utah, receiving a Ph.D. Degree in Physical Chemistry in 1976;

Since 1988, I have been employed by InSite Vision Inc., where I have been engaged in research and development in the field of pharmaceutical development, focusing on the development of ophthalmic drug products;

I am an inventor of the above-identified application;

I am familiar with Davis et al, Bright et al, WO 95/09601 and Curatolo et al and I am familiar with the rejections in the above-identified application based on

WO 95/09601 and Curatolo et al and based on Davis et al and Bright et al, which are set forth in the Office Actions dated April 24, 2002 and August 19, 2002;

WO 95/09601

The following statements are submitted in order to demonstrate that the compositions disclosed in WO 95/09601 are not considered to one of ordinary skill in the art to be topical ophthalmic compositions:

Example I of WO 95/09601 (syringeable gel composition):

The gel of Example I of WO 95/09601 is non-aqueous. This gel could not be placed in the eye for the following reasons:

The gel would adsorb all of the water from the tear fluid, and surrounding eye tissues, which would cause a massive toxic response;

Glycerol monooleate, which is present in the gel at a high percentage, is an irritant to the eye even at low concentrations; and

Azithromycin, which is present in the gel at the concentration of 25 wt. % would illicit a toxic response in the eye.

Example II of WO 95/09601 (sustained release composition):

The sustained release composition of Example II of WO 95/09601 could not be placed in the eye for the following reasons:

Propylene carbonate, which is present in the sustained release composition, cannot be used in the eye because it is an irritant to the eye;

Azithromycin, which is present in the gel at the concentration of 30 wt. %, will be toxic to the eye if the release rate of the drug from the matrix is not appropriately controlled. If the drug is released rapidly, the maximum tolerable concentration of azithromycin in the eye will be exceeded; and

The extruded and formed shapes capable of being inserted into subgingival cavities with pliers are not suitable for insertion into an eye.

Example III of WO 95/09601 (oral tablet):

The oral tablet of Example III of WO 95/09601 can not be placed in the eye for the following reasons:

An oral tablet would not be inserted into an eye; and

Azithromycin, which is present in a typical capsule in the amount of 250 mg., is a concentration of azithromycin that is toxic to the eye.

Example IV of WO 95/09601 (mouth wash):

The mouth wash composition of Example IV of WO 95/09601 can not be placed in the eye for the following reasons:

ETOH, which is present in the mouth wash composition at a concentration of 16.24 wt% (200 proof), cannot be used in the eye at a level over 3 ppm because it will denature the corneal epithelium and illicit a toxic response;

Glycerin, which is present in the mouth wash composition at a concentration of 10 wt%, will yield an aqueous solution with an osmotic pressure well above 1000 mOsm. This concentration will also cause dehydration of the cornea;

The type of flavor in the mouth wash composition is not particularly specified in Example IV. Flavors can be irritating or toxic to the eye. The eye does not sense flavors and therefore flavors are not used in topical ophthalmic compositions;

The mouth wash composition contains benzoic acid/sodium benzoate, a preservative that cannot be used in the eye because it is an irritant to the eye; and

The mouth wash composition contains dyes. Dyes can be toxic to the eye. Some dyes are also dissolved in organic solvents, which cannot be used in the eye. Colors are generally not used in topical ophthalmic compositions because they can interfere with vision and can stain the conjunctiva of the eye.

In view of the above analysis and the knowledge in the art related to ophthalmology, I conclude that the compositions taught and disclosed in WO 95/09601 are not be suitable for topical use in the eye and are not be considered to be topical ophthalmic compositions.

Curatolo et al

The following statements are submitted in order to demonstrate that the compositions disclosed in Curatolo et al are not considered to one of ordinary skill in the art to be topical ophthalmic compositions:

Tablet components and oral suspension components are not intended for the eye. Examples 1-5 and 8-10 of Curatolo et al relate to tablets or capsules.

Examples 1-3 of Curatolo et al

Further, Example 1, 2 and 3 are capsule formulations which containing corn starch, lactose and magnesium stearate/sodium lauryl sulfate. Corn starch is not used in the eye because it forms an opaque solution and can precipitate. Lactose is not used in the eye at such high concentrations, which will cause the osmolality to far exceed a tolerable range in the eye. The sulfate/stearate are lubricants to prevent caking of the granulation and are not used in the eye. These materials also have limited water solubility and are not useful in aqueous formulations. Additionally, the azithromycin drug concentrations are too high to be safely used in the eye.

Example 4 of Curatolo et al

Example 4 adds calcium phosphate at a concentration that will be extremely basic and not acceptable to the eye. Example 4 also contains sodium croscarmellose, which cannot be used in the eye because it contains titanium dioxide an abrasive plus dyes and triacetin which can cause eye irritation.

Example 5 of Curatolo et al

Example 5 adds Opadry, which is a tablet coating that contains titanium dioxide plus polyethyleneglycol (PEG). Titanium dioxide is an abrasive and PEG can be an irritant.

Example 6 and 7 of Curatolo et al

Examples 6 and 7 are oral suspensions which cannot be applied to the eye because the drug concentrations are too high for eye tolerance. Examples 6 and 7 also contain sucrose, which causes the osmolality to be above tolerable limits, silicon dioxide, which is an abrasive, and flavoring, which are not added to ophthalmic formulations.

Examples 8-10 of Curatolo et al

Examples 8, 9 and 10 are tablet formulations which are not acceptable for the administration to the eye. They contain components, which as described above, are not suitable for use in the eye or formulated at concentrations above eye tolerability limits.

Examples 11 through 13 of Curatolo et al

The pH of the suspensions of Examples 11 through 13 is 10, which is not acceptable for ophthalmic delivery. At a pH of 10, the corneal will be degraded much the same as would happen if a basic compound like sodium hydroxide is spilled into an eye

Example 11

The concentration of this powder to be added to water is not specified. The concentration of sucrose and sorbitol when added to water are be sufficiently high to cause the formulation to be above the osmolality of the eye, which would lead to toxic effects on eye tissues. The titanium dioxide and silicon dioxide are not used in the eye because they are abrasives, which can cause corneal abrasions. Additionally, they would serve no useful purpose in an ophthalmic composition. Flavors are not used in the eye as previously stated. The exact pH of the suspension can be too high due to the addition of sodium carbonate, which is also the case in other oral suspensions described in Curatolo et al. Tragacanth gum powder is not used in the eye and the effect would be unknown. Gum is used as a thickener for oral formulations.

Examples 12 and 13

In Examples 12 and 13, the sucrose/sorbitol is greater than 8-10% in the final suspension, which will exceed the osmolality limit of the eye. Osmotic pressures greater than 400 mOsm cannot be tolerated in the eye.

With no other component in the oral suspension, a sucrose/sorbitol level of 8-10% in solution would produce an osmotic pressure much greater than 1000 mOsm. With the other components in the oral suspensions described in Examples 12-13, the osmotic pressure would be even greater.

The suspensions of Examples 12 and 13 contain silicon dioxide. Silicon dioxide is not known to be used in the eye as described above;

The suspensions of Examples 12 and 13 contain flavorings and dyes. Flavorings and dyes are not used in the eye as discussed above.

Example 14 of Curatolo et al

Additional unit dose oral suspension formulations are disclosed in Example 14 of Curatolo et al. The drug concentration, sucrose or sorbitol, silicon dioxide and spray dried flavors are used in oral formulations, but cannot be used in ophthalmic formulations as stated above.

Oral formulations are not ophthalmic formulations and cannot be used in the eye for the reasons outlined above.

In view of the above analysis and the knowledge in the art related to ophthalmology, I conclude that the compositions taught and disclosed in Curatolo et al are not suitable for topical use in the eye and are not be considered to be topical ophthalmic compositions.

Davis et al and Bright et al

The following statements are submitted in order to demonstrate the knowledge in the art concerning the properties of azithromycin:

As discussed on page 5 of the specification of the above-captioned application, azithromycin exhibits an improved acid-stability, half-life and cellular uptake in tissues over erythromycin;

Acid stability is a property desired in treatment via an oral dosage form because oral dosage compositions must pass through the gastric acid environment of the stomach. The drug must survive acid conditions in the stomach at a sufficient concentration to be absorbed to become effective as use as an antibiotic.

Acid stability for gastric acid environments is not a property required in topical ophthalmic compositions.

High cellular uptake and retention via oral administration allows for systemic delivery of azithromycin to the site of the infection. The high cellular uptake of azithromycin is thought to be due to tissue binding in cells;

Oral administration leads to systemic circulation of the drug due to the partition of the drug into the tissue;

Systemic exposure to azithromycin following ocular topical application is extremely low;

Oral administration also leads to phagocytic delivery. The phagocytic delivery of azithromycin, while an important factor for systemic infection treatment by oral dosing, does not play any significant role in treating ocular infection using topical administration;

From the known half-life in tissue data, one of ordinary skill in the art could not predict that azithromycin is suitable for use in the eye by topical administration for at least the following two reasons:

1) The bacteria for which azithromycin is a systemically targeted are different from bacteria which cause infections in the eye. Even if some of the same bacteria are found in the eye, the strains are generally different resulting in different bacterial sensitivities; and

2) Since different bacteria and strains exist in the eye, drug levels to kill or inhibit the bacteria are different. It was not known in the art if sufficient levels of azithromycin could be obtained by topical administration since systemic and topical administration result in different targeted tissue levels. Bacteria for systemic indications and ocular indications are shown in Table 1 and 2.

Table I: Bacteria for Ocular Infection taken from PDR for Quixen

Aerobic Gram-positive microorganisms

Corynebacterium species *
Staphylococcus aureus (methicilin-susceptible strains only)
Streptococcus pneumoniae
Streptococcus (Groups C/F)
Streptococcus (Group G)
Viridans group streptococci

Aerobic Gram-negative microorganisms

Acinetobacter lwoffi*
Haemophilus influenzae
Serratia marcescens*

Table 2: Bacteria for azithromycin taken from PDR for Zithromax

Aerobic Gram-positive microorganisms

Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most Strains of Enterococcus faecalis and methacillin-resistant staphylococci are resistant to Azithromycin.

Aerobic Gram-negative microorganisms

Haemophilus influenzae
Moraxella catarrhalis

"Other" Microorganisms

Chlamydia trachomatis
Beta-lactamase production should have not effect on Azithromycin activity.
Azithromycin has been shown to be active in *in vitro* and in the prevention and treatment of disease caused by the following microorganisms:

Mycobacteria

Mycobacterium avium complex (MAC) consisting of:
Mycobacterium avium
Mycobacterium intracellular.

Azithromycin is more charged molecule than erythromycin. The greater the charge of a drug, the lower the conjunctival and corneal permeation. Thus, one of ordinary skill in the art would expect that azithromycin would penetrate less when administered to the eye as compared to erythromycin. Therefore, one skilled in the art could not predict if azithromycin could achieve effective drug levels in the eye by topical administration for effective inhibition of bacteria of the eye.

In view of the knowledge in the art concerning the properties of azithromycin, the known properties of azithromycin would not be a sufficient reason or motivation for one of ordinary skill in the art to substitute azithromycin for erythromycin in topical ophthalmic compositions or in a process for treating an eye. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 12/18/02

Lyle M. Bowman